55. (Previously Presented) The respiratory mask assembly of claim 54, wherein the mask frame includes a front wall portion defining a forward end of the mask frame, the front wall portion having a circular gas inlet aperture configured to connect to a gas delivery conduit.

56. (Previously Presented) The respiratory mask assembly of claim 55, wherein the mask frame includes a rim defining a rearward end of the mask frame and being configured to allow a cushion to be attached thereto.

57. (Previously Presented) The respiratory mask assembly of claim 54, wherein each of the female connector portions includes a first wall structure that is disposed between respective side wall portions, each of the first wall structures and the side wall portions having an inward end portion and an outward end portion defining a direction that extends generally radially outwardly relative to the circular gas inlet aperture.

58. (Previously Presented) The respiratory mask assembly of claim 57, wherein the first wall structure includes at least one recess extending therethrough configured to cooperate and receive the at least one resiliently biased locking element of the respective male connector portion.

59. (Previously Presented) The respiratory mask assembly of claim 54, wherein the pair of female connector portions are formed in one piece with the mask frame.

60. (Previously Presented) A respiratory mask and headgear combination comprising a respiratory mask having a rigid mask frame, headgear for securing said mask on a patient, said headgear including at least one attachment strap, said mask frame having rigidly secured thereto a first connector portion, and a second connector portion on said strap adapted for releasable mating with said first connector portion, wherein

said first and second connector portions form a press-release connection between said mask frame and said strap;

one of said first and second connector portions is a female connector;

the other said first and second connector portions is a corresponding male connector: and

one of the first and second connector portions is formed in one piece with the mask frame.

61. (Previously Presented) The respiratory mask and headgear combination of claim 60, wherein said male connector includes a resiliently biased cantilever member depending from a leading end portion of said male connector, said cantilever member including a locking element that releasably engages with a recess formed in the female connector.

62. (Previously Presented) A respiratory mask for use with a headgear having first connector portions thereon, each of the first connector portions having one of a resiliently biased locking element and a locking element receiving aperture, the respiratory mask comprising:

a mask frame including a front wall portion defining a forward end of the mask frame, the front wall portion having a circular gas inlet aperture configured to connect to a gas delivery

conduit, the mask frame including a pair of inclined side wall portions and a base portion configured in a generally triangular arrangement so as to define an upper vertex portion provided by an intersection of the inclined side wall portions and a pair of laterally spaced lower vertex portions provided by intersections of respective inclined side wall portions and the base portion, each side wall portion and the base portion having a portion thereof connected to the front wall portion; an extension member protruding generally radially outwardly relative to the circular gas inlet from the upper vertex, the extension member being configured to be coupled to a forehead support; the extension member providing an arcuate front wall member having a slot formed therein being oriented parallel to the extension member;

the mask frame includes an annular rim extending generally outwardly from rear edges of the inclined side wall portions and the base portion, the rim defining a rearward end of the mask frame and being configured to allow a cushion to be attached thereto;

a pair of second connector portions formed in one piece with the mask frame at respective lower vertex portions thereof, the second connector portions being configured to releasably engage with the first connector portions; wherein

each of the second connector portions includes a generally oblong slot, the generally oblong slot being formed by a base wall member that is disposed between a respective side wall portion and the base portion of the mask frame and being generally parallel to the front wall portion, a pair of parallel spaced opposing wall members extending generally perpendicularly from the base wall member, and structure disposed between the pair of spaced opposing wall members and being spaced from and generally parallel to the base wall member, the structure includes the other of the resiliently biased locking element and locking element receiving aperture; the base and opposing wall members and the structure having inward end portions and

outward end portions defining a direction that extends generally radially outwardly relative to the circular gas inlet aperture; outward end portions of the base wall member and the opposing wall structures defining a generally C-shaped laterally facing surface contained within a single plane.

63. (Previously Presented) A respiratory mask assembly comprising:

a headgear structure including at least one elongate strap, one end of the elongate strap being doubled over to form a loop;

a pair of first connector portions attached to the elongate strap, each of the first connector portions including a trailing portion that has a pair of spaced side portions and a cross bar extending transversely therebetween to define a strap receiving aperture configured to allow the strap to pass therethrough so that the crossbar is disposed within the loop of the strap, each of the first connector portions also including a leading portion that has a pair of longitudinally extending side beams spaced slightly inwardly from the side portions, leading edge portions of the side beams being inwardly tapered toward the leading edges thereof, each of the first connector portions having one of a resiliently biased locking element and a locking element receiving aperture;

a mask frame including a front wall portion defining a forward end of the mask frame, the front wall portion having a circular gas inlet aperture configured to connect to a gas delivery conduit, the mask frame including a pair of inclined side wall portions and a base portion configured in a generally triangular arrangement so as to define an upper vertex portion provided by an intersection of the inclined side wall portions and a pair of laterally spaced lower vertex portions provided by intersections of respective inclined side wall portions and the base portion, each side wall portion and the base portion having a portion thereof connected to the front wall

portion; an extension member protruding generally radially outwardly relative to the circular gas inlet from the upper vertex, the extension member being configured to be coupled to a forehead support; the extension member providing an arcuate front wall member having a slot formed therein being oriented parallel to the extension member;

the mask frame includes an annular rim extending generally outwardly from rear edges of the inclined side wall portions and the base portion, the rim defining a rearward end of the mask frame and being configured to allow a cushion to be attached thereto;

a pair of second connector portions formed in one piece with the mask frame at respective lower vertex portions thereof, the second connector portions being configured to releasably engage with the first connector portions; wherein

each of the second connector portions includes a generally oblong slot, the generally oblong slot being formed by a base wall member that is disposed between a respective side wall portion and the base portion of the mask frame and being generally parallel to the front wall portion, a pair of parallel spaced opposing wall members extending generally perpendicularly from the base wall member, and structure disposed between the pair of spaced opposing wall members and being spaced from and generally parallel to the base wall member, the structure including the other of the resiliently biased locking element and the locking element receiving aperture; the base and opposing wall members and the structure having inward end portions and outward end portions defining a direction that extends generally radially outwardly relative to the circular gas inlet aperture; outward end portions of the base wall member and the opposing wall structures defining a generally C-shaped laterally facing surface contained Within a single plane;

wherein the side beams of each first connector portion are capable of being passed through the oblong slot of the respective second connector portion, such that the side beams are

disposed substantially between the base wall member and the structure and are disposed substantially between and parallel to the pair of spaced opposing wall members, the crossbar being disposed proximate and generally parallel to the outward end portions of the base wall member;

the resiliently biased locking elements being movable between deflected and undeflected positions and being resiliently biased toward the undeflected position; and

the locking element receiving apertures being configured to locking engage with the resiliently biased locking elements when in the undeflected position.

64. (Currently Amended) A respiratory mask and headgear combination comprising:

a respiratory mask assembly, said mask assembly having rigidly secured thereto a first connector portion, said mask assembly further including a second connector portion adapted for releasable mating with said first connector portion; and

adjustable headgear to secure said mask assembly on a patient, said headgear including at least one attachment strap, wherein

at least one of said first and second connector portions ~~form~~ includes an elastically movable component which defines in part a quick-release connection to release the at least one attachment strap from said mask assembly;

said first connector portion and said second connector portion are releasably lockable with respect to one another; and

a selected connector portion of said first and second connector portions is integrally formed in one piece with the mask assembly.

65. (Previously Presented) A respiratory mask and headgear combination according to claim 64, wherein the respiratory mask is a nasal mask.

66. (Previously Presented) A respiratory mask and headgear combination according to claim 64, wherein the mask assembly includes a frame, and the selected connector portion is provided in one piece with the frame.

67. (Previously Presented) A respiratory mask according to claim 64, wherein the mask assembly includes a frame, and the selected connector portion is positioned adjacent a gas inlet aperture of the frame.

REMARKS/ARGUMENTS

Claims 21-67 are pending. By this Amendment, claims 38, 43 and 64 are amended. Reconsideration in view of the above amendments and the following remarks is respectfully requested.

At the outset, Applicants respectfully submit that all of claims 1-20 were canceled upon filing of the present application. Claims 2-20, specifically, were canceled in box 14 of the application transmittal.

Claims 11, 12, 13, 28-30 and 64-67 were rejected under 35 U.S.C. § 102(b) over Feeney (WO 87/01950). This rejection is respectfully traversed. At the outset, the rejection of claims 11-13 is not addressed as those claims have been canceled.

With regard to claim 28, Feeney fails to teach or suggest a mask frame and a pair of female connector portions formed in one piece with the mask frame and being configured to receive the male connector portions therein. Instead, Feeney discloses a pair of mounting posts 14 on each side of mask frame 14. The mounting posts are not female connector portions, as recited in claim 28. Furthermore, Feeney's connecting elements which are attached to each end of the headgear straps do not constitute male connector portions, as recited in claim 28.

With regard to claim 64, Feeney does not teach or suggest a respiratory mask and headgear combination in which one of the first and second connector portions includes an elastically movable component which defines in part a quick-release connection to release the at least one attachment strap from the mask assembly, wherein the first connector portion and the second connector portion are releasably lockable with respect to one another and a selected connector portion of the first and second connector portions is integrally formed in one piece with the mask assembly.

Instead, Feeney teaches a cylindrical post 14 which receives a circular aperture provided in the connector portion provided to each end of the headgear straps.

Dependent claims 29, 30 and 65-67 are patentable by virtue of their dependency on claims 28 and 64, respectively.

Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 21, 39, 41, 47, 48 and 60 were rejected under 35 U.S.C. § 103(a) over Feeney in view of Tuman (U.S. Patent No. 5,205,832). This rejection is respectfully traversed.

With respect to claim 21, neither Feeney nor Tuman teaches or suggests that a female connector is formed in one piece with the mask frame. Instead, Feeney teaches a male connector, i.e., post 14, which is formed in one piece with the mask frame. Tuman does not make up for this deficiency. Moreover, Tuman essentially teaches the arrangement as shown in Prior Art Figure 2a of the present application in which both connection elements are provided along an intermediate portion of the headgear. In other words, both connector portions are connected to floppy headgear straps, each of which may become mispositioned during the mask assembly process.

Similarly, neither Feeney nor Tuman teaches or suggests that the first connector portion is a female connector formed in one piece with the mask frame, as recited in claim 39. Even if the frame of Feeney is considered to be a female connector portion, the end connector portions of Feeney's head strap cannot be considered corresponding male connectors, as set forth in claim 39.

With regard to the rejection of independent claims 41, 48 and 60, Applicants respectfully submit that the Patent Office is relying on impermissible hindsight. One of ordinary skill in the art considering the combined disclosures of Feeney and Tuman would not arrive at the subject

matter set forth in claims 41, 48 and 60. In particular, there is no teaching or suggestion to provide Tuman's press release connection to Feeney's connection mechanism, absent the use of impermissible hindsight. Tuman merely shows the arrangement shown in Prior Art Figure 2a of the present invention, whereby each end of a floppy strap is provided with a connector portion which together form a press release connection. The disadvantages of this approach are described in the present specification. There is simply no motivation to make one of Tuman's connector portions integral with the Feeney frame.

Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 21-67 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of U.S. Patent No. 6,374,826. Applicants respectfully traverse the rejection because the Office Action has not identified any differences between the patented and pending claims, and there is no statement that one of ordinary skill in the art would have been motivated to modify the patented claims, i.e., by removing or adding features, to arrive at the subject matter of the present application claims.

Reconsideration and withdrawal of the rejection are respectfully requested.

Applicants appreciate the indication that claims 62 and 63 define patentable subject matter. However, in view of the above amendments and remarks, Applicants respectfully submit that all the claims are patentable and that the entire application is in condition for allowance.

Should the Examiner believe that anything further is desirable to place the application in better condition for allowance, he is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

NIXON & VANDERHYE P.C.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

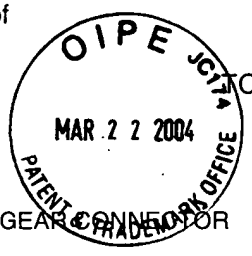
In re Patent Application of

GUNARATNAM et al.

Serial No. 10/090,173

Filed: March 6, 2002

Title: MASK AND HEADGEAR CONNECTOR



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TC/A.U. 3743

Examiner: Mital Patel

Date: March 22, 2004

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Sir:

RESPONSE/AMENDMENT/LETTER

This is a response/amendment/letter in the above-identified application and includes an attachment which is hereby incorporated by reference and the signature below serves as the signature to the attachment in the absence of any other signature thereon.

☐ **Correspondence Address Indication Form Attached.**

Fees are attached as calculated below:

Total effective claims after amendment **47** minus highest number previously paid for **47** (at least 20) = 0 x $ 18.00	$	0.00
Independent claims after amendment **11** minus highest number previously paid for **10** (at least 3) = 1 x $ 86.00	$	86.00
If proper multiple dependent claims now added for first time, add $290.00 (ignore improper)	$	0.00
Petition is hereby made to extend the current due date so as to cover the filing date of this paper and attachment(s) ($110.00/1 month; $420.00/2 months; $950.00/3 months)	$	420.00
Terminal disclaimer enclosed, add $ 110.00	$	0.00
☐ First/second submission after Final Rejection pursuant to 37 CFR 1.129(a) ($770.00) ☐ Please enter the previously unentered , filed ☐ Submission attached	$	0.00
Subtotal	$	**506.00**
If "small entity," then enter half (1/2) of subtotal and subtract ☐ Applicant claims "small entity" status. ☐ Statement filed herewith	-$	0.00
Rule 56 Information Disclosure Statement Filing Fee ($180.00)	$	0.00
Assignment Recording Fee ($40.00)	$	0.00
Other:		**0.00**
TOTAL FEE ENCLOSED	$	**506.00**

The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Account No. 14-1140. A duplicate copy of this sheet is attached.

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NIXON & VANDERHYE P.C.
By Atty: Paul T. Bowen, Reg. No. 38,009

Signature: _____

[0043] While glycyrrhizin has been used as a flavoring additive in foods and in the pharmaceutical industry for years, the present invention is directed to its use to form complexes with active ingredients to improve the solubility of poorly water soluble active ingredients. These glycyrrhizin complexes have been characterized by spectroscopic, chemical, and physical measurements. The active ingredient-glycyrrhizin complexes have surprisingly improved water solubilities. In one embodiment of the invention, optimized formulations of glycyrrhizin for specific basic drugs have been shown to improve their water-solubility. In some cases the water solubility of the drug is improved by over 50 fold.

[0044] As a consequence of their improved solubilities, the complexes can be conveniently incorporated into a wide variety of compositions and dosage forms. The dosage forms of the invention allow considerable flexibility in the treatment of patients. Owing to the wide range of available dosage forms of the invention, the optimized route of delivery can be tailored for a particular drug depending on its requirements for delivery. For example, some drugs require rapidly delivery to a patient's blood stream to reach the desired therapeutic effect. A highly water soluble complex and a fast releasing dosage form of the present invention provides these advantages. The pharmacokinetic limitations of particular drugs may also be overcome because of the wide variety of dosage forms of the invention. For example, water soluble dosage forms now provided by the invention can deliver a drug solution parenterally to avoid first-pass metabolism effects.

[0045] The water-solubility of weakly basic active agents is dramatically improved through their incorporation into the glycyrrhizin complex. The solubility of famotidine, for example, is increased as it is incorporated into a complex with glycyrrhizin, as shown in the solubility phase diagram of Figure 2. The saturated water solubility of famotidine alone is less than 1 mg/mL while the water solubility of the famotidine complex can reach as high as 50 mg/mL. Another poorly-water-soluble basic active agent, the anti-anxiety agent, buspirone, can also be rendered more water soluble through glycyrrhizin complexation. As graphically illustrated in Figure 3, the water-solubility of buspirone was increased from 0.38 mg/mL, for buspirone alone, to 44 mg/mL through complexation with glycyrrhizin. Figure 4 illustrates the solubility phase diagram of loratadine by adding glycyrrhizin. The solubilities of two other active agents, caffeine and sildenafil were also found to increase 6 and 200 fold, respectively, through complexation with glycyrrhizin.

[0046] In a preferred embodiment of the invention the famotidine/glycyrrhizin complex has a water solubility of at least 10 mg/mL, preferably at least 30 mg/mL. For buspirone, a preferred embodiment of the invention provides for a buspirone/glycyrrhizin complex with a solubility of at least 5 mg/mL, preferably at least 20 mg/mL. For sildenafil, in a preferred embodiment the solubility of its complex with glycyrrhizin is at least 2 mg/mL, preferably at least 10 mg/mL.

[0047] Figure 5 shows the pH-reversibility of complexation of a famotidine-glycyrrhizin complex of the present invention. As the pH is reduced, the complex breaks apart into its constituents (glycyrrhizin and the poorly soluble famotidine). At still lower pH, the famotidine is protonated and becomes more water soluble. Thus, the complex is expected to dissociate in the stomach when orally ingested thereby releasing the famotidine so that there is no reduction in absorption.

[0048] Any active agent that has low water solubility and can form a complex with glycyrrhizin by accepting its proton(s) or forming hydrogen bond with the glycyrrhizin is suitable for the present invention. These active ingredients include, for example, compounds that contain moieties such as linear and heterocyclic amines, amides, imines, imides and nitriles. The present invention is applicable, but not limited to, drugs that are in the following therapeutic categories: abortifacients, ACE inhibitors (for example, lisinopril and quinapril), adrenocorticotropic hormones, alpha-adrenergic agonists (for example, phenylpropanolamine and pseudoephedrine), alpha-adrenergic blockers (for example, labetalol and terazosin), alpha-glucosidase inhibitors (for example, acarbose and miglitol), anabolic steroids (for example, pizotyline), narcotic analgesics (for example, codeine and dextromoramide), non-narcotic analgesics (for example, phenazopyridine and acetaminophen), anorexics (for example, fenfluramine and phentermine), anthelmintics (for example, quinacrine and mebendazole), antiallergics (for example, astemizole and azelastine), antialopecials (for example, finasteride and minoxodil), antiamebics (for example, chloroquine and chlortetracycline), antianginals (for example, acebutolol and gallopamil), antiarrhythmics (for example, amiodarone and penbutolol), antiarthritics (for example, hydroxychloroquine and chloroquine), antiasthmatics (for example, azelastine and ketotifen), antibiotics (for example, trimethoprim and neomycin B), anticholinergics (for example, poldine and procyclidine), anticonvulsants (for example, beclamide and carbamazepine), antidepressants (for example, clomipramine and dothiepin), antidiabetics (for example, glibornuride and glipizide),

antidiarrheals (for example, defenoxin and diphenoxylate, antidotes (for example, neostigmine and tacrine), antidyskinetics (for example, amantadine and cabergoline), antiemetics (for example, buclizine and chlorpromazine), antiestrogens (for example, raloxifene and tamoxifen), antifungals (for example, terbinafine and nystatin), antiglaucoma agents (for example, betaxolol and carteolol), antigonadotropins (for example, danazol), antigout agents (for example, allopurinol and sulfinpyrazone), antihistaminics (for example, astemizole and azatadine), antihyperlipoproteinemics (for example, bezafibrate and colestipol), antihypertensives, (for example, acebutolol and indoramin), antihypothyroids (for example, liothyronine), nonsteroidal antiinflammatories (for example, indomethacin and piroxicam), antimalarials (for example, amodiaquine and halofantrine), antimigraines (for example, dolasetron and pizotyline), antineoplastics (for example, anastrozole and etoposide), antiparkinsonians (for example, amantadine and benserazide), antipheochromocytoma agents, antipneumocystis, antiprostatic hyperplasia agent, antiprotozoals (for example, amodiaquine and metronidazole), antipruritics (for example, cyproheptadiene), antipsoriatics (for example, methotrexate), antipsychotics (for example, benperidol and flupentixol), antipyretics (for example, acetaminophen), antirickettsials (for example, tetracycline), antispasmodics (for example, flavoxate and mebeverine), antithrombocythemics (for example, anagrelide), antithrombotics (for example, cilostazol and ticlopidine), antitussives (for example, dextromethorphan), antiulceratives (for example, famotidine and omeprazole), antivirals (for example, amantadine and zidovudine), anxiolytics (for example, buspirone, lorazepam and medazepam), aromatase inhibitors (for example, aminoglutethimide and anastrozole), benzodiazepine antagonists, beta-adrenergic antagonists (for example, ephedrine and ritodrine), beta-adrenergic blockers (for example, acebutolol and atenolol), bradycardic agents, bronchodilators (for example, albuterol and ephedrine), calcium channel blockers (for example, amlodipine and flunarizine), carbonic anhydrase inhibitors (for example, dichlorphenamide), cardiotonics, choleretics, cholinergics (for example, neostigmine), cholinesterase inhibitors (for example, galanthamine), cholinesterase reactivators, CNS stimulants (for example, chlorphentermine and diethylpropion), cytoprotectants (for example, irsogladine), decongestants (for example, phenylpropanolamine), diuretics (for example, cimetidine and xipamide), dopamine receptor agonists (for example, quinagolide and ropinirole), dopamine receptor antagonists (for example, bromocriptine and ropinirole), ectoparasiticdes (for example, lufenuron), emetics, expectorants (for example, carbocysteine),

fibrinogen receptor antagonists, gastric proton pump inhibitors (for example, lansoprazole), gastric secretion inhibitors (for example, omeprazole), gastroprokinetics (for example, cisapride), hemostatics, histamine H_2 receptor antagonists (for example, cimetidine), immunomodulators (for example, levamisole), immunosuppressants (for example, cyclophosphamide), keratolytics, leukotriene antagonists (for example, zafirlukast), miotics (for example, pilocarpine), MAO inhibitors (for example, selegiline and tranylcypromine), mucolytics (for example, carbocysteine and tasuldine), muscle relaxants (for example, flurazepam and mebeverine), mydriatics, narcotic antagonists (for example, naltrexone), nootropics (for example, bifemelane and idebenone), oxytocics (for example, ergonovine), potassium channel activators (for example, nicorandil), respiratory stimulants (for example, tacrine), sedatives and hypnotics (for example, chlordiazepoxide and clomethiazole), serenics (for example, eltoprazine), serotonic receptor agonists (for example, buspirone and methysergide), serotonic receptor antagonists (for example, granisetron and nefazodone), serotonin uptake inhibitors (for example, fluoxetine and sertraline), thrombolytics, tocolytics (for example, ritodrine), vasodilators (for example, flunarizine and oxprenolol), and vasoprotectants (for example, naftazone). Preferred drug substances include those intended for oral administration and transmucosal delivery where taste masking and/or solubility is a problem. The description of these therapeutic categories and a list of basic drugs can be found in DRUGS, Synonyms & Properties, edited by G. W. A. Milne, Ashgate Publishing Company, England, 2000.

[0049] The therapy using these drugs preferably involves an on-demand release of the active agent. These on-demand active ingredients include, for instance, gastrointestinal, anti-emetics, anti-motion sickness, anti-allergy, anti-diarrheals and respiratory drugs. Gastrointestinal drugs, such as H_2-receptor antagonists famotidine, ranitidine and cimetidine can be used to treat the symptoms associated with peptic ulcers. Other examples include anti-diarrheals such as loperamide, anti-emetics such as granisetron and dimenhydramine and anti-allergy drugs such as loratadine.

[0050] Another preferable class of agents that are also on-demand agents include cyclic GMP phosphodiesterases such as sildenafil which is used to treat erectile dysfunction.

[0051] A molar ratio between active agent and glycyrrhizin ranging from 3:1 to 1:1 is preferred.

[0052] In addition to the active agent and glycyrrhizin that dosage forms may incorporate additional ingredients. These additional ingredients include, for example, preservatives, chelating agents, surfactants, taste modifiers, buffering agents, antacids, plasticizers, water soluble fillers, water insoluble fillers, binders, glidants, film formers, enteric coatings, solvents, coloring agents, thickening agents, osmotic agents, and semi-permeable membrane-forming agents.

[0053] Preservatives include anti-microbial agents and non-organic compounds are exemplified by sodium benzoate, parabens and derivatives, sorbic acid and its salts, propionic acids and its salts, sulfur dioxide and sulfites, acetic acid and acetates, nitrides and nitrates.

[0054] Chelating agents include edetic acid and its salts (disodium, tetrasodium, calcium disodium), diethylenetriaminepentaacetic acid and its salts (DTPA), hydroxyethylenediaminetriacetic acid and its salts (HEDTA) and nitilotriacetic acid (NTA). Preferably, the dosage forms of the present invention can general include 0 to 5% by weight of chelating agents.

[0055] Taste modifiers include flavoring agents, sweetening agents and taste masking agents and are exemplified by: the essential oils or water-soluble extracts of menthol, wintergreen, peppermint, sweet mint, spearmint, vanillin, cherry, chocolate, cinnamon, clove, lemon, orange, raspberry, rose, spice, violet, herbal, fruit, strawberry, grape, pineapple, peach, kiwi, papaya, mango, coconut, apple, coffee, plum watermelon, nuts, durean, green tea, grapefruit, banana, butter, chamomile, sugar, dextrose, lactose, mannitol, sucrose, xylitol, maltitol, acesulfame potassium, talin, sucralose, aspartame, saccharin, sodium saccharin, sodium cyclamate, and honey. Preferably, the dosage forms of the present invention can include 0 to 10% taste modifiers on a weight basis.

[0056] Buffering agents include acidulants and alkalizing agents exemplified by citric acid, fumaric acid, lactic acid tartaric acid, malic acid, as well as sodium citrate, sodium bicarbonate, and carbonate, sodium or potassium phosphate, and magnesium oxide. Preferably, the dosage forms of the present invention can include 0 to 80% buffering agents on a weight basis.

[0057] Antacids include aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, aluminum magnesium hydroxide and

sodium bicarbonate. Preferably, the dosage forms of the present invention can include 0 to 50% antacids on a weight basis.

[0058] Plasticizers include glycerin, sorbitol, propylene glycol, polyethylene glycol, triacetin, triethyl citrate (TEC), acetyl triethyl citrate (ATEC) and other citrate esters. Preferably, the dosage forms of the present invention can include 0 to 40% plasticizers on a weight basis.

[0059] Fillers include microcrystalline cellulose, lactose, starch and derivatives, polyols (such as mannitol, sorbitol, xylitol), calcium phosphates and calcium sulfates. Preferably, the dosage forms of the present invention can include 0 to 70% fillers on a weight basis..

[0060] Binders include cellulose derivatives, povidone, polyvinylpyrrolidone, gelatin, natural gums and starch derivatives. Preferably, the dosage forms of the present invention can include 0 to 10% binders on a weight basis.

[0061] Glidants include talc, starch, alkali stearates, microcrystalline cellulose and colloidal silicon dioxide. Preferably, the dosage forms of the present invention can include 0 to 1% glidants on a weight basis.

[0062] Bioadhesive film formers include water soluble nonionic polymers such cellulose derivatives such as carboxymethylcellulose, hydroxyethyl cellulose, methylcellulose, hydroxypropyl cellulose and hydroxypropyl methylcellulose; polyvinylpyrrolidone; polyvinyl alcohol; polyethylene oxide; modified starch; gelatin; agar; locust bean gum; bentonite and scheroglucan; preferably polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinyl alcohol, gelatin, polyethylene oxide; most preferably, polyvinyl alcohol, gelatin and hydroxypropyl methylcellulose. Water soluble anionic polymers suitable for use with the present invention include, but are by no means limited to, polyacrylic acid such as carbopol, polycarbophil, poly(methyl vinyl ether-co-methacrylic acid), poly(2-hydroxyethyl methacrylate), poly(methylmethacrylate), poly(isobutylcyanoacrylate), poly(isohexycyanoacrylate) and polydimethylaminoethyl methacrylate; acacia; alginate; carrageenan; guar gum derivative; karaya gum; pectin; tragacanth gum; xanthan gum; dextran; sodium carboxymethylcellulose ("sodium CMC") and hyaluronic acid; preferably carbopol, polycarbophil, alginate, carrageenan, pectin and sodium CMC; most preferably carbopol, polycarbophil, alginate,

carrageenan and sodium CMC. The anionic polymer or combination of anionic and noniomic polymers included in the bioadhesive, film preferably contains 10 to 60 wt% of an anionic polymer or combination of aniomic and nonionic polymers. Preferably, the dosage forms of the present invention can include 0 to 90% film formers on a weight basis.

[0063] Enteric coatings include methacrylic acid methacrylic acid ester copolymers (Eudragit), cellulose acetate phthlate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethyl ethylcellulose and hydroxypropyl methylcelulose acetate succinate. Preferably, the dosage forms of the present invention can include 0 to 30% enteric coatings on a weight basis.

[0064] Solvents include water and ethanol. Preferably, the dosage forms of the present invention can include 0 to 80% solvents on a weight basis.

[0065] Coloring agents include FD&C coloring agents, natural coloring agents, and natural juice concentrates, pigments such as titanium oxide, silicon dioxide, and zinc oxide. Preferably, the dosage forms of the present invention can include 0 to 5% coloring agents on a weight basis.

[0066] Thickening agents include natural gums, cellulose derivatives, polyacrylic acid (Carbomer) and polyvinyl alcohol. Preferably, the dosage forms of the present invention can include 0 to 15% thickening agents on a weight basis.

[0067] Osmotic agents include simple eletrolytes (sodium chloride, potassium choride), water soluble sugars (fructose, sucrose, dextrose, sorbitol, xylitol) and polyglycols. Preferably, the dosage forms of the present invention can include 0 to 60% osmotic agents on a weight basis.

[0068] Semi-permeable, membrane-forming agents include polyvinyl alcohol, polyurethane, cellulose acetate, ethylcellulose and polyvinyl chloride. Preferably, the dosage forms of the present invention can include 0 to 30% semi-permeable, membrane-forming agents on a weight basis.

[0069] Emulsifying agents include solubilizers and wetting agents and are exemplified by polyvinyl alcohol, sorbitan esters, cyclodextrins, benzylbenzoate, glyceryl monostearate, polyoxyethylene alkyl ethers, polyoxyethylene stearates, poloxamer, polyoxyethylene castor oil derivatives, hydrogenated vegetable oils, bile salts, polysorbates

and ethanol. Preferably, the dosage forms of the present invention can include 0 to 10% emulsifying agents on a weight basis.

[0070] Stabilizers include anti-oxidants, chelating agents, and enzyme inhibitors as exemplified by ascorbic acid, vitamin E, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), propyl gallate, dilauryl thiodipropionate, thiodipropionic acid, gum guaiac, citric acid, edetic acid and its salts and glutathione. Preferably, the dosage forms of the present invention can include 0 to 15% by weight of the stabilizers.

[0071] The glycyrrhizin complexes can be prepared by any method that provides active agent/glycyrrhizin complexes with high water solubility. One embodiment is illustrated in Figure 6. Glycyrrhizin is first dissolved or dispersed in an aqueous or hydroalcoholic solvent, preferably with suitable amounts of preservatives. The aqueous solvent is preferably water. The hydroalcoholic solvent includes water with a water soluble alcohol such as ethanol, methanol or isopropanol. Then, active agent, preferably as a powder, is gradually added into the glycyrrhizin solution or gel under agitation to result in a clear complex solution. The resulting complex solution can then be spray-dried or spray-coated with enteric polymers. The resulted complex powders are palatable (licorice-flavored), hygroscopic and highly water-soluble.

[0072] The resulted complexes can be formulated into various delivery systems to improve patient compliance, increase dissolution rate and control release rate. Preferred delivery systems include all oral dosage forms, nasal spray and inhalation. The oral dosage forms are palatable with high water solubility, fast dissolution and rapid absorption. These delivery systems include re-constituted powders packed in soluble and edible film sachets, solution for oral and/or parenteral administration, re-constituted enteric microcapsules for suspensions, troches, lozenges, effervescent tablets, chewable tablets, intraoral fast-dissolving films, fast-dissolving intraoral wafers, nasal liquid spray, nasal powder spray, inhalation powder, mucoadhesive devices for buccal, rectal and vaginal administration, osmotic tablets and capsules containing enteric microcapsules.

[0073] In another embodiment the invention relates to methods of treating diseases by administering a dosage form containing a highly water-soluble complex of an active agent and glycyrrhizin. More particularly what is provided is a method for treating an individual with an ulcer by administering a dosage form containing a highly water-soluble drug complex

of an H_2 receptor antagonist and glycyrrhizin. A preferred method for treating an ulcer uses famotidine as the H_2-receptor antagonist in the dosage form of the invention. A more preferred method includes a method of treating an individual wherein the ratio of famotidine to glycyrrhizin on a molar basis is 3:1 to 1:1. The dosage forms administered to the individual include, for instance, tablets (including chewable tablets), effervescent tablets, lingual films and fast-dissolving tablets.

[0074] Also provided is a method of treating sexual dysfunction by administering a dosage form containing a drug complex of sildenafil and glycyrrhizin to an individual.

[0075] The present inventions include a method of treating seasonal allergy by administering a dosage form containing a complex of loratadine and glycyrrhizin to an individual.

[0076] Further provided is a method of treating anxiety by administering a dosage form containing a drug complex of buspirone and glycyrrhizin to an individual.

[0077] The dose of the dosage form or composition of the present invention as an active agent will be determined by the physician based on the weight, age and physical condition of the patient. In general, the dose of the composition or dosage form of the present invention will be equal to or less than the standard dose of the free active agent.

Examples

[0078] Some preferred embodiments of the present invention will now be further described through the following examples set forth hereinbelow which are intended to be illustrative of the preferred embodiments of the present invention and are not intended to limit the scope of the invention as set forth in the appended claims.

Example 1: Re-constituted powders packed in soluble and edible film sachet

[0079] 27 grams of monoammonium glycyrrhizin and 33 grams of famotidine were dissolved in 1140 grams of 50% ethanol-water mixture. The resulting solution was then spray-dried to obtain famotidine/glycyrrhizin complex powder. 30 grams of complex powder was blended with 1 gram of cherry flavor powder, 1 gram of acesulfame potassium and 44 grams of sorbitol. The resulted powder, 92 mg as a unit weight, was filled in the water soluble and edible film sachet which is made from 10 mg of propylene glycol and 50 mg of

HPMC with 2 mil thickness. The resulted sachet, which contains 20 mg of Famotidine, could be directly dropped into water to reconstitute aqueous solution or taken orally with or without drinking any water.

Example 2: Solution dosage form

[0080] 13.1 grams of monoammonium glycyrrhizin and 6.1 grams of famotidine were dissolved in 138.8 grams of water. The resulting solution was then spray-dried to obtain famotidine/glycyrrhizin complex powder. 0.6 grams of the complex powder was dissolved in 65.85 grams of water, 0.02 grams of Nipagin M/Nipasol M(methylparaben /propylparaben, weight ratio 4:1), 0.02 grams of sodium ethylenediaminetetraacetic acid (EDTA), 0.01 grams of Cremaphor RH40 polydyoxyethylated castor oil, 0.5 grams of Cherry ice, 1 gram of acesulfame potassium, 30 grams of sorbitol, and 2 grams of polyvinylpyrrolidone were added into the solution and resulted in a homogenous solution. The final solution contains 0.2% (w/w) famotidine.

Example 3: Re-constituted enteric microcapsules for suspensions

[0081] 54 grams of monoammonium glycyrrhizin and 66 grams of famotidine were dissolved in 2280 grams of 50% ethanol-water mixture. 40 grams of cellulose acetate phthalate and 0.4 gram of propylene glycol was dissolved in 2359.6 grams of 1:1 acetone/ethanol. The complex solution was spray-dried and counter-spray-coated with the cellulose acetate phthalate solution to obtain enteric coated famotidine/glycyrrhizin complex microparticles. The core to shell ratio is 3:1. 80 grams of microparticles were well blended with 1 gram of acesulfame potassium, 1 gram of cherry flavor powder and 18 grams of sorbitol. The resulted powder, 120 mg, was packed into a unit pouch. Each pouch contains 40 mg famotidine.

Example 4: Effervescent tablets

[0082] 27 grams of monoammonium glycyrrhizin and 33 grams of famotidine were dissolved in 1140 grams of 50% ethanol-water mixture. The resulting solution was then spray-dried to obtain famotidine/glycyrrhizin complex powder. 20 grams of the complex powder was well blended with 1 gram of cherry flavor powder, 1 gram of acesulfame potassium, 39.7 grams of citric acid, 30.3 grams of sodium bicarbonate, 5 grams of mannitol, 2 grams of Methocel E5 (hydroxypropyl methylcellulose) and 1 gram of talc. The resulted

powder was directly compressed into tablets with a unit weight of 180 mg. Each tablet contains 20 mg Famotidine.

Example 5: Chewable tablets

[0083] 27 grams of monoammonium glycyrrhizin and 33 grams of famotidine were dissolved in 1140 grams of 50% ethanol-water mixture. The resulting solution was then spray-dried to obtain famotidine/glycyrrhizin complex powder. 30 grams of the complex powder was well blended with 1 gram of cherry flavor powder, 1 gram of acesulfame potassium, 50 grams of mannitol, 13 grams of microcrystalline cellulose, 4 grams of Methocel E5 and 1 gram of talc. The resulted powder mixture was directly compressed into tablets with a unit weight of 120 mg. Each tablet contains 20 mg of famotidine.

Example 6: Intraoral fast dissolving film

[0084] 67.5 grams of monoammonium glycyrrhizin and 82.5 grams of famotidine were dissolved in 2350 grams of 50% ethanol-water mixture. The resulting solution was then spray-dried to obtain famotidine/glycyrrhizin complex powder. 6 grams of the complex powder, 0.01 gram of Nipagin M/Nipasol M, 0.015 gram of sodium EDTA, 1 gram of propylene glycol, 0.5 gram of peppermint oil and 3 grams of Methocel E15 were dissolved in 35 grams of 50% ethanol-water mixture to form homogenous and viscous solution for coating. The coating solution was casted at 20 mil and dried at 40 °C to remove water and ethanol. The resulted dry film with an estimated 2% of residual water was cut to suitable size and shape for unit dose pouching. the film weight ranges from 32 to 35 mg. Each film contains 10 mg Famotidine.

Example 7: Fast dissolving intraoral wafer

[0085] 80 grams of monoammonium glycyrrhizin and 40 grams of famotidine were dissolved in 1080 grams of water. The resulting solution was then spray-dried to obtain famotidine/glycyrrhizin complex powder. 60 grams of the complex powder, 0.1 gram of Nipagin M/Nipasol M, 0.1 gram of sodium EDTA, 1 gram of propylene glycol, 1.4 gram of peppermint flavor, 1.4 gram of acesulfame potassium, 24 grams of mannitol, and 12 grams of Methocel E5 were dissolved in 500 grams of water. The resulted homogenous solution was dispersed into molded blister packaging sheet for freeze drying process to remove water and

result in fast dissolving intraoral wafer. The unit weight is 50 mg. Each wafer contains 10 mg famotidine.

Example 8: Osmotic tablets

[0086] 80 grams of monoammonium glycyrrhizin and 40 grams of famotidine were dissolved in 1080 grams of water. The resulting solution was then spray-dried to obtain famotidine/glycyrrhizin complex powder. 30 grams of the complex powder was well blended with 10 grams of sodium bicarbonate, 3 grams of Methocel E5, 1 gram of talc and 50 grams of potassium chloride. The resulted powder was directly compressed into osmotic cores. A suspension of micronized lactose/cellulose acetate/triethyl citrate in a weight ration of 2/2/1 in ethanol/dichloromethane in a weight ratio of 10.5/31.5 was prepared and sprayed onto the tablet cores in a pan coater. A laser was used to drill the release orifice of coated tablet. Each tablet, 200 mg, contains 20 mg famotidine.

Example 9: Capsules containing enteric microcapsules

[0087] 54 grams of monoammonium glycyrrhizin and 66 grams of famotidine were dissolved in 2280 grams of 50% ethanol-water mixture. 40 grams of cellulose acetate phthalate and 0.4 gram of propylene glycol was dissolved in 2359.6 grams of 1:1 acetone/ethanol. The complex was spray-dried and counter-spray-coated with the cellulose acetate phthalate solution to obtain enteric coated famotidine/glycyrrhizin complex microparticles. The core to shell ratio is 3:1. 40 grams of the resulted complex microparticles were then well blended with 30 grams of calcium carbonate, 19 grams of microcrystalline cellulose, and 1 gram of talc. The resulted powder mixture, 220 mg, was filled into a hard gelatin capsule. Each capsule contains 40 mg famotidine.

Example 10: Glycyrrhizin - Famotidine Complex; solubility improvement

[0088] 10 ml of glycyrrhizin ammonium solution/dispersion, concentration ranged from 0.015 M to 0.1 M, were prepared using distilled water in 20 ml scintillation vials. 750 mg of Famotidine was added into each vial. The control study was conducted with zero concentration of glycyrrhizin. Four studied solutions and the control were mounted on a vertical rotator with a rotation speed of 10 rpm under room temperature for 24 hours. The supernatant of each vial was taken using a 5 ml syringe and filtered through a 0.45 um syringe filter. Discarded first three drops and collected 1 ml of filtrate in HPLC vial. Diluted

each filtrate, 1/10 or 1/100, with distilled water. Diluted filtrates were analyzed by HPLC. The resulted concentration, mg/ml, is plotted as Figure 2.

Example 11: Glycyrrhizin - Buspirone Complex; solubility improvement

[0089] 10 ml of glycyrrhizin ammonium solution/dispersion, concentration ranged from 0.012 M to 0.083 M, were prepared using distilled water in 20 ml scintillation vials. 500 mg of Buspirone base was added into each vial. The control study was conducted with zero concentration of glycyrrhizin. Four studied solutions and the control were mounted on a vertical rotator with a rotation speed of 10 rpm under room temperature for 24 hours. The supernatant of each vial was taken using a 5 ml syringe and filtered through a 0.22 um syringe filter. Discarded first three drops and collected 1 ml of filtrate in HPLC vial. Diluted each filtrate, 1/10 or 1/100, with distilled water. Diluted filtrates were analyzed by HPLC. The resulted concentration, mg/ml, is plotted as a Figure 3.

Example 12: Glycyrrhizin - Famotidine Complex; reversibility

[0090] 20 ml of glycyrrhizin/famotidine complex solution (12 mg/ml) was prepared. The solution pH was measured using Orion pH meter while 0.1 N HC1 was gradually added into the solution drop-by-drop under stirring condition. During titration, 1 ml sample was taken, filtered, diluted and analyzed at pHs 5.35, 4.5, 4.0, 2.8, 2.0 and 1.0. The results are plotted as Figure 5.

Example 13: Glycyrrhizin - Loratadine Complex; solubility improvement

[0091] 10 ml of glycyrrhizin ammonium solution/dispersion, concentration ranged from 0.01 M to 0.03 M, were prepared using distilled water in 20 ml scintillation vials. 50 mg of Loratadine was added into each vial. The control study was conducted with zero concentration of glycyrrhizin. Three studied solutions and the control were mounted on a vertical rotator with a rotation speed of 10 rpm under room temperature for 24 hours. The supernatant of each vial was taken using a 5 ml syringe and filtered through a 0.22 um syringe filter. Discarded first three drops and collected 1 ml of filtrate in HPLC vial. Diluted each filtrate, 1/10 or 1/100, with distilled water. Diluted filtrates were analyzed by HPLC. The resulted concentration, mg/ml, is plotted as Figure 4.

Example 14: Glycyrrhizin - Sildenafil Complex; solubility improvement

[0092] 10 ml of 0.1 M glycyrrhizin ammonium solution/dispersion was prepared using distilled water in 20 ml scintillation vials. 500 mg of sildenafil base was added into each vial. The control study was conducted with zero concentration of glycyrrhizin. Studied solution and the control were mounted on a vertical rotator with a ration speed of 10 rpm under room temperature for 24 hours. The supernatant of each vial was taken using a 5 ml syringe and filtered through a 0.45 μm syringe filter. Discarded first three drops and collected 1 ml of filtrate in HPLC vial. Diluted each filtrate, 1/10 or 1/100 with distilled water. Diluted filtrates were analyzed by HPLC. The solubility of sildenfil was improved more than 200 fold.

Example 15: Glycyrrhizin - Caffeine Complex; solubility improvement

[0093] 10 ml fo 0.1 M glycyrrhizin ammonium solution/dispersion was prepraed using distilled water in 20 ml scintillation vials. 500 mg of caffeine base was added into each vial. The control study was conducted with zero concentration of glycyrrhizin. Studied solution and the control were mounted on a vertical rotator with a ration speed of 10 rpm under room temperature for 24 hours. The supernatant of each vial was taken using a 5 ml syringe and filtered through a 0.45 μm syringe filter. Discarded first three drops and collected 1 ml of filtrate in HPLC vial. Diluted each filtrate, 1/10 or 1/100 with distilled water. Diluted filtrates were analyzed by HPLC. The solubility of caffeine was improved more than 5 fold.

[0094] The present invention having been disclosed in connection with the foregoing embodiments, additional embodiments will now be apparent to persons skilled in the art. The present invention is not intended to be limited to the embodiments specifically mentioned, and accordingly reference should be made to the appended claims rather than the foregoing discussion, to assess the spirit and scope of the present invention in which exclusive rights are claimed.